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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,938	02/23/2007	Chunyan Song	EX04-037C-US	7049

63572 7590 03/01/2010

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
03/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,938	SONG ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,13-15 and 18-25* is/are pending in the application.

4a) Of the above claim(s) *4,5,7,13-15 and 18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 12/29/09.

Claims 11, 12, and 16 were canceled.

Claims 1-10, 13-15, and 20-25 remain pending.

Claims 4, 5, 7, 13-15, and 20-25 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/13/09. Claims 18 and 19 were withdrawn from consideration by Applicants amendment filed 5/13/09.

Claims 1-3, 6, and 8-10 are under consideration in this Office Action.

This Action is NON-FINAL due to a new ground of rejection not necessitated by amendment.

After further consideration, the enablement rejection in the Action of 6/29/09 is withdrawn. Further search and consideration has revealed that those of skill in the art at the time of the invention accepted that RANBP2 is a functional homolog of Drosophila nup358 (see e.g. Forler et al (Mol. Cell. Biol. 24(3): 1155-1167, 2/204)). Moreover, the disclosure in the specification that inhibition of RANBP2 led to nuclear retention of FOX0 establishes a nexus between a PTEN pathway and RANBP2 (see e.g. Wang et al (Chem. & Biol. 11: 16-18, 2004).

Oath/Declaration

The Oath/Declaration stands objected to for the reasons of record. Applicant's indication that a new Oath/Declaration will be submitted is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6, and 8-10 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 6, and 8-10 are indefinite because it is unclear what are the metes and bounds of the claim term "RANBP2" e.g. in steps (c) and (d). The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. Further, it is unclear if Applicant intends RANBP2 to embrace terms such as RANBP2L1, which is the designation for a divergent duplication of a RANBP2 locus (see Northwang et al (Genomics 47: 383-392, 1998)). Amending the claims to specifically and uniquely identify RANBP2 polypeptides and polynucleotides by SEQ ID NOS can obviate the rejection.

Claims 1-3, 6, and 8-10 are indefinite in their recitation of "the PTEN/IGF pathway" and "PTEN/IGF function". The Office acknowledges that the terms IGF and

PTEN are well known in the art. However, the term PTEN/IGF pathway is not a term of art. Moreover, it was known at the time of the invention that PTEN and IGFs involved in extremely complex signaling networks that overlap. Because of the complexity of these networks, it is unclear to which pathway "the PTEN/IGF pathway" refers. Furthermore, it is unclear what are the metes and bounds of this term. For example, it is known that PTEN inhibits telomerase activity in endometrial cancer cells by decreasing hTERT mRNA (Zhou et al (Gyn. Oncol. 101:305-310, 2006), and that IGF-1 stimulates hTERT activity in prostate cancer cells (Wetterau et al (J. Clin. Endocrinol. Metab. 88(7): 3354-3359, 2003). Would one of skill in the art then conclude that hTERT expression is part of a PTEN/IGF pathway in both of these cell types? In all cell types? It seems that one of skill would not arrive at this conclusion for all cell types because the relationship between hTERT and PTEN/IGF has not been established in all cells. Thus it cannot be known what the term "PTEN/IGF pathway" means for all cells.

It is also not clear what are the metes and bounds of "PTEN/IGF function". Is this term limited to the specific catalytic and binding functions of PTEN and the specific binding functions of IGFs? Or, is it meant to encompass all that occurs in pathways that are regulated by both PTEN and IGF? For example, is altered hTERT expression considered to be a defective PTEN/IGF function? For the purpose of examination the Office has interpreted "PTEN/IGF function" broadly to include e.g. altered hTERT expression. See rejection under 35 USC 103, below.

Response to Arguments

Applicant's arguments filed 12/29/09 have been fully considered but they are not persuasive.

Applicant notes that the claims have been amended to require a system comprising any of SEQ ID NOS: 1-6, and asserts that this overcomes the rejection. This is not persuasive. Claim steps (c) and (d) require determining expression of RANBP2 in the system, or providing a second system that expresses RANBP2. These steps do not identify the specific RANBP2 to be assayed or expressed. Accordingly, it is not clear which RANBP2 is to be assayed or expressed. This rejection could be overcome by amending step (c) to require detecting expression of said RANBP2 comprising any one of SEQ ID NOS: 1-6, and by inserting "said" immediately prior to subsequent instances of the word "RANBP2".

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 3, 6, 8, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forler et al (Mol. Cell. Biol. 24(3): 1155-1167, 2/204) in view of Yokoyama et al (Nature 376: 184-188, 1995) as evidenced by Shin et al (Cancer Lett. 287: 231-239, 2010), Yu et al (EMBO J. 28:21-33, 2009), Honegger et al (J. Biol. Chem. 261(2): 569-575, 1986), Zhou et al (Gyn. Oncol. 101:305-310, 2006), Wetterau et al (J.

Clin. Endocrinol. Metab. 88(7): 3354-3359, 2003), and Tao et al (FEBS Letters 454: 312-316, 1999).

Forler inhibited expression of RANBP2 in Drosophila S2 cells by RNA interference and showed that this resulted in complete inhibition of cell proliferation. See Fig. 1(f).

Forler did not teach inhibition of any of SEQ ID NOS: 1-6.

Yokoyama studied the structure and function of human RANBP2, using cultured human (HeLa) cells. It would have been obvious to one of ordinary skill in the art at the time of the invention to extend the studies of Forler to human cells, such as the HeLa cells of Yokoyama, because the function of RANBP2 in human cells was clearly of interest, as evidenced by Yokoyama. Absent evidence to the contrary, the HeLa cells of Yokoyama encode RANBP2 of SEQ ID NO: 1, i.e. they are wild type for RANBP2. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention to inhibit expression of RANBP2 in the cells of Yokoyama using an RNA interference molecule comprising an antisense oligomer, essentially as taught by Forler. This would require developing an RNAi agent specific for human RANBP2. It would have been obvious to first test different RNAi agents in order to select one that functioned well to decrease RANBP2 expression in HeLa cells, thus rendering obvious steps a-c of the claims.

It then would have been obvious to use the selected RNAi agent to examine in detail the effects of RANBP2 inhibition on cellular proliferation in the HeLa cells of Yokoyama in order to determine if the same effects were observed as in the S2 cells of

Forler. Note that HeLa cells comprise active IGF receptors and active PTEN as evidenced by Shin (page 235, section 3.6) and Yu et al at page 24, left column, first full paragraph). Moreover it was clear from Shin that HeLa cells are cultured in media containing fetal bovine serum (see page 233, section 2.2), which inherently contains IGF-1 (see Honegger, abstract). Thus, it would have been obvious to assay cellular proliferation of the HeLa cells in the presence of IGF-1. Absent evidence to the contrary, the measurement of changes in cellular proliferation would serve as a measurement of changes in IGF/PTEN signaling, and the invention as a whole was prima facie obvious.

Claim 3 is included in this rejection because it is known in the art that HeLa cells overexpress telomerase (See Tao, abstract, and paragraph bridging columns on page 312), and that telomerase expression is modulated by PTEN (see Zhou, abstract) and by IGF (see Wetterau, abstract). Accordingly telomerase expression is a function of the PTEN/IGF pathway, and HeLa cells are considered to have defective PTEN/IGF function because they have inappropriate telomerase expression. The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10

USPQ2d 1922, 1923 (BPAI 1989), and MPEP 2112(V), 2112.01(I), and 2112.02. It is noted that the instant claims are not product claims, but the issue here is whether or not a recited product (cultured cells with defective PTEN/IGF function) are equivalent to the a prior art product (HeLa cells with defective control of telomerase expression).

Claim 10 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Forler et al (Mol. Cell. Biol. 24(3): 1155-1167, 2/204) and Yokoyama et al (Nature 376: 184-188, 1995) as applied to claims 1, 2, 3, 6, 8, and 9 above and further in view of Sokoloff et al (US 7071163).

The teachings of Forler and Yokoyama render obvious a method of identifying in HeLa cells an RNAi agent that inhibits RANBP2, and then assaying the effect of that agent on cellular proliferation in the presence of IGF-1.

These references did not teach a PMO.

Sokoloff taught that interfering RNA and morpholino antisense nucleic acids were functional alternatives as expression inhibitors (paragraph bridging columns 12 and 13), and taught that synthetic oligomers could contain phosphorodiamidate backbones (column 11, lines 36-39).

It would have been obvious to one of ordinary skill in the art at the time of the invention use an antisense PMO oligomer in the method rendered obvious by Forler and Yokoyama because Sokoloff taught that gene expression could be inhibited by alternative means including RNA interference and antisense oligonucleotides. In view of the teachings of Sokoloff, it was routine in the art to modify antisense oligomers,

either as siRNA strands or more classical antisense agents, with PMO linkages. One would have been motivated to make such modification in order to improve the stability of the oligomer. Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Fereydoun Sajjadi, can be reached at (571) 272-3311. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635